

**REMARKS**

**Status of Claims**

Claims 23 - 26 and 28 -47 remain pending in the application. The Examiner's withdrawal of prior art rejections is gratefully acknowledged.

**Information Disclosure**

Any confusion resulting from failure to provide complete naming identity between NPL item 4 of the last submitted IDS and the transmitted reference is regretted. Submitted herewith is a further copy of the renamed reference and a further IDS, which lists only the single reference not considered.

**Rejections under 35 USC §112, first paragraph**

The examiner has now given a written description rejection on the asserted basis that the claim contains subject matter not described in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The Examiner has identified the claims as including a step of removing endotoxin by filtering through a series of filters including a glass fiber filter and a nylon filter but has characterized these claimed filters as a "broad genus" of any glass or nylon filter. The Examiner further states that while the specification discloses filtration through a .2 µm filter for certain vendors (Pall-Filtration, Sartorius and Gelman), made of glass or nylon, there is no disclosure of filters other than this size and these vendors that would have the property of removing endotoxins without nucleic acid loss. Thus, the Examiner has concluded that the inventors, at the time the specification was filed, did not have possession of the allegedly broad genus of removing endotoxin from a plasmid DNA solution comprising filtration through any glass or nylon filter as need to practice the claimed invention.

As with prior rejections on various grounds in this case, the new written description rejection is surprising in light of the fact that claims to glass fiber and nylon filters without vendor or size limitations have been pending since 08-29-2003 (see claims 27 and 28) and yet this is the first time a written description rejection on this basis has appeared. Nonetheless, the Examiner's close attention to any potential written description issues is appreciated as well as the present

opportunity to respectfully but firmly traverse the rejection on both legal and technical and bases.

A description as originally filed is presumed to be adequate, unless or until evidence or reasoning to the contrary has been presented by the examiner sufficient to rebut the presumption. *See MPEP § 2163.04.* It is respectfully argued that the Examiner has not accorded the presumption of sufficiency to Applicants and has focused on a genus –species argument that might find purchase in analysis of a nucleic acid claim but is inapt to the methods of plasmid purification claims at issue.

As to written description generally, in the new PTO Written Description Training Materials (Rev. 1, March 25, 2008), it is clarified that the Examiner must determine whether one of skill in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing including by the following considerations:

- a. Actual reduction to practice
- b. Disclosure of drawings or structural chemical formulas
- c. Sufficient relevant identifying characteristics, such as:
  - i. Complete structure
  - ii. Partial structure
  - iii. Physical and/or chemical properties
  - iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure
- d. Method of making the claimed invention
- e. Level of skill and knowledge in the art
- f. Predictability in the art

As to the above factors, the following facts support that one of skill in the art would conclude that the applicants were in possession of the claimed methods for plasmid purification, including endotoxin removal using the unique combination of glass and nylon filtration.

- a. Working example 5 presents plasmid purification using nylon and glass filters in series to reduce bacterial load and reduce endotoxin.
- b. One of skill in the art clearly understands what is meant by both glass and nylon, these being known compounds with discrete chemical characteristics. Thus one of skill in the art is able to visualize or recognize filters having these characteristics. Glass and nylon are known chemical constituents that fully define the claimed filter

types as select species of the broad genus of filters. The identifying characteristic of the claimed species of glass and nylon is this very chemical makeup. It is noted in this context, that the written description is met for chemicals where the specification literally describes the claimed compounds by structure or name, in the instant case, glass and nylon filters as both disclosed and claimed.

- c. The Examiner has argued that there is no description of identifying characteristics for recognizing that a particular filter from a particular manufacturer will have the claimed property of removing endotoxins. To the theoretical possibility that there may in fact be some unsuitable glass or nylon filters, such can be readily determined by one of skill in the art standing on the shoulders of the present disclosure. To wit, a plasmid DNA preparation containing a certain level of endotoxin can be run over the test filters and the level determined afterwards relative to any loss of plasmid DNA. This correlation between structure and function is so straightforward as to not require elaboration.
- d. Detailed methods of practicing the claimed methods are provided including working examples.
- e. The level of skill and knowledge in the art is high and routine experimentation is often, if not typically, undertaken to identify suitable sources for a particular commodity utilized in the art

Regarding the genus – species arguments of the Examiner, it is firmly argued that neither nylon nor glass constitute a genus in the context of the claim but are rather specific limited chemical constituent species from the genus of filters.

Furthermore, the specification does not disclose the single porosity 0.2  $\mu\text{m}$  but also discloses 0.45 $\mu\text{m}$  or larger: “Pall Ultipor N<sub>66</sub> filters and Sartorius Sartorpure GF filters have been found to remove substantial endotoxin with high yield of nucleic acid. Preferably, the nucleic acid solution is pre-filtered through a nominal 0.2  $\mu\text{m}$  or a 0.45  $\mu\text{m}$  or larger filter before filtration through an absolute 0.2  $\mu\text{m}$  filter. Glass and nylon filters are preferred.” *See [0058]* of the published application. Clearly the porosity of the filters is not the critical feature and to limit the claims in such way would deny the inventors a scope of protection commensurate with the disclosed advances to the art.

Although not required, working example 5 presents plasmid purification using nylon and glass filters in series to reduce bacterial load and reduce endotoxin. One of skill in the art would

conclude that the applicants were in possession of the claimed methods for plasmid purification, including endotoxin removal using the unique combination of glass and nylon filtration.

It is noted that, in contrast with endotoxin removal, for purposes of ultrafiltration a number of different chemical membrane constituents are disclosed as suitable including cellulose acetate, polysulfone, polyethersulfone and polyvinylidene difluoride. *See [0051]* of the published application.

As previously explained, the technical problem of endotoxin removal is particularly difficult as it pertains to plasmid solutions. Endotoxin is a negatively charged molecule. Thus, the prior art indicates the use of positively charged filter media to remove endotoxins. *See Gerba and Hou, Endotoxin Removal by Charge-Modified Filters, Applied and Environmental Microbiology vol. 50 (6) (1985) p 1375 – 1377*, previously submitted. Plasmids represent pure strands of DNA and, by virtue of the phosphate backbone of the DNA, are also negatively charged molecules. Thus, one of skill in the art trying to purify plasmid DNA from a solution including endotoxins was confronted with the problem that both endotoxins and DNA are negatively charged such that a media that is able to remove one of these molecules is potentially able to remove the other as well because these molecules share charge characteristics.

The present claimed invention involves a specific combination of steps for plasmid purification including filtration through specific media including glass fiber and nylon filters. The claimed glass fiber and nylon filters are not functioning merely as inert screens for debris and contaminants. It is believed that endotoxins are removed by binding to the glass fiber and nylon supports, which surprisingly did not bind the plasmid DNA passing over them. Applicants found that this filtration step resulted in significant purification, particularly through the removal of endotoxins, and that this step, as well as the combined method claimed, is of particular importance in the purification of plasmid DNA at pharmaceutical scale because significant removal of plasmid DNA was not attendant to the same filtration steps that resulted in removal of endotoxin. The methods disclosed and claimed in the present application have been shown to be particularly effective in manufacturing plasmid preparations of high purity

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and yield at pharmaceutical scale as evidenced by commercial application and success in the field.

**Conclusion**

For the reasons stated herein, the Applicant respectfully submits that independent claims 23, 33, 37 and 43 are allowable and that the dependent claims are, in turn, also allowable. Applicant respectfully requests allowance of the claims at an early date. The Commissioner is authorized to charge any additional fees incurred in this application or credit any overpayment to Deposit Account No. 50-1922. Should the Examiner have any questions, please do not hesitate to call Applicant's attorney at 832-446-2421.

Respectfully submitted,



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